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09/763,590	02/26/2001	Kazunari Tara	04853/0059	8733

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EXAMINER	
LAGOR, ROBERT KARL	

ART UNIT	PAPER NUMBER
1637	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/763,590	TAIRA ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *8,9 and 12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5, 10*.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal of the lack of unity of Group I and II is on the ground(s) that the ribozymes of Group II comprise a common core structure with the ribozymes of Group I because the ribozymes of Group II, comprising SEQ ID NO:2, have the same nucleic acid sequence as the ribozymes of Group I, plus 6 additional residues. These arguments have been found to be persuasive because the search for SEQ ID NO:1 would also provide a search for SEQ ID NO:2 and the ribozymes of Group I and II do comprise a common core structure. Therefore, Group II is rejoined with Group I.

The traversal of the lack of unity of Group I and Group III is on the ground(s) that the ribozymes of Group III comprise significant portions of SEQ ID NO:1 and SEQ ID NO:2 and therefore would not present a serious burden to be searched along with the ribozymes of Group I. This has not been found to be persuasive because the ribozymes of Group III, ribozymes comprising SEQ ID NO:4, do not comprise the common core structure of the ribozymes of Group I, that is, SEQ ID NO:1. Although the ribozymes of Group II comprise portions of SEQ ID NO:1 and 2, a search for SEQ ID NO:1 would not provide art for SEQ ID NO:4 because there is significant structure (ie. sequence) differences and, therefore, would require a separate search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 8, 9 and 12-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-7, 10 and 11 have been examined on the merits.

Drawings

The corrected or substitute drawings were received on 01-13-2003. These drawings are acceptable.

Specification

The amendment filed 01-13-2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: A substitute sequence listing was filed on 01-13-2003, wherein the sequences submitted for SEQ ID NO:1 and SEQ ID NO:2 have been changed as compared to the original disclosure. Specifically, each of SEQ ID NO: 1 and 2 the sequence provided in the sequence listing has been truncated by one uracil residue (u) at the 3' terminus as compared to the sequence in

the originally filed specification. This further results in new matter within the specification at each recitation of SEQ ID NO: 1.

Applicant is required to cancel the new matter in the reply to this Office Action.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the sequences labeled as SEQ ID NO: 1 and 2 do not match the sequences provided in the sequence listing, as discussed above in the objection to the specification.

Additionally, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because in figure 2 there are sequences that have not been labeled by the appropriate SEQ ID NO.

In order to be fully responsive to this Office action, the application must comply fully with the requirements of 37 CFR 1.821 through 1.825.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 are indefinite because they recite SEQ ID NO:1 and SEQ ID NO:2, but also recite sequences associated with those SEQ ID NO's wherein the sequence does not match the sequence provided in the sequence listing. It is unclear which sequences are being claimed, the sequences recited in the claims or the sequences recited in the sequence listing.

Claims 10 and 11 are indefinite because they are dependent upon a non-elected claim.

Claim 10 is further indefinite because of the recitation of a variant consisting of residues 1-80 of SEQ ID NO:1, wherein the variant is according to claim 8, which recites a variant consisting of the secondary structure represented by SEQ ID NO:4, a 95 residue nucleic acid. It is unclear how a molecule consisting of 80 residues can provide a secondary structure of 95 residues, further, it is unclear how SEQ ID NO:1 could have the same secondary structure as SEQ ID NO:4, since the sequence of a nucleic acid determines the secondary structure and SEQ ID NO:1 and 4 do not have the same sequence. It is unclear what molecule is being claimed in claim 10.

Claim 11 is further indefinite because of the recitation of a variant consisting of residues 1-86 of SEQ ID NO:2, wherein the variant is according to claim 8, which recites a variant consisting of the secondary structure represented by SEQ ID NO:4, a 95 residue nucleic acid. It is unclear how a molecule consisting of 86 residues can provide

a secondary structure of 95 residues, further, it is unclear how SEQ ID NO:2 could have the same secondary structure as SEQ ID NO:4, since the sequence of a nucleic acid determines the secondary structure and SEQ ID NO:2 and 4 do not have the same sequence. It is unclear what molecule is being claimed in claim 11.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1-7, 10 and 11 recite SEQ ID NO: 1 and/or SEQ ID NO: 2. The sequences of SEQ ID NO: 1 and SEQ ID NO: 2 provided by the amended sequence listing (filed 01-13-2003) are different than the sequences provided in the originally filed specification and claims. No support for the altered sequences was found in the originally filed specification or claims and, therefore, SEQ ID NO: 1 and 2 are considered to be new matter.

Claims 3, 4, 5, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a ribozyme by

transcribing a vector in vitro (cell culture), a method of cleaving mRNA in vitro (cell culture) and a composition comprising a ribozyme or vector and a pharmaceutically acceptable carrier, does not reasonably provide enablement for a method of making a ribozyme by transcribing a vector in vivo (whole organism), a method of cleaving mRNA in vivo (whole organism) and a pharmaceutical composition comprising a ribozyme or vector expressing the ribozyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 3-7 are directed to methods of making a ribozyme by transcribing a vector and cleaving a target RNA using a ribozyme, including a target HIV-1RNA. The specification contemplates practicing these methods in vivo (whole organism) for the treatment of disease, including the treatment and prevention of HIV. Additionally, these claims are targeted to pharmaceutical compositions comprising a ribozyme, or vector expressing the ribozyme. Pharmaceutical compositions are included in this rejection, since the claimed compositions would be required to have a pharmaceutical activity.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The specification provides examples wherein the claimed ribozyme expressed from a vector cleaves RNA in vitro in HeLa cells. The specification demonstrates that the claimed ribozymes localized in the cytoplasm of cells in vitro, as did the HIV target RNA. The specification does not demonstrate that the claimed ribozymes can be delivered in vivo (whole organism) at a concentration effective to cleave the target RNA or provide a pharmaceutical effect or a treatment for any disease, including HIV. The specification does not demonstrate that a vector expressing the claimed ribozyme can be delivered to a target cell in vivo (whole organism) or maintain expression of the ribozyme at a level effective to cleave target RNA, or provide any pharmaceutical or treatment effect for a disease, including HIV.

At the time the instant invention was made, the therapeutic use of oligonucleotides, including ribozymes and vectors, was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of

ribozymes and other nucleic acids for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects." These same issues would be expected to apply to ribozyme therapies, as well.

Gene therapy methods encounter many of the same obstacles as other nucleic acid based therapies with respect to delivery, for example, but have the additional issues of random integration into host NDA, poor expression levels, unexpected loss of expression, difficulties in determining proper promoter enhancer combinations for cell (see for example, Anderson, WF and Verma et al.)

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein antisense is delivered to cells *in vitro* and HIV RNA is cleaved and replication is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of ribozymes, differences in target site accessibility,

cellular uptake differences and the potential for non-specific side effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Ribozymes would have the same problems, as they are structurally similar to antisense.

The fields of ribozymes and gene therapy, to date, do not provide guidelines by which ribozymes and vectors expressing ribozymes can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver the claimed ribozymes or vectors expressing said ribozymes to a target cell or tissue *in vivo* (whole organism) at a concentration effective to provide a pharmaceutical effect or to cleave RNA, including HIV RNA.

In order to practice the invention claimed, over the full scope claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of how to specifically deliver the claimed ribozymes or vectors expressing a ribozyme to a target cell *in vivo* (whole organism) at a concentration effective to result the cleavage of an RNA, including HIV RNA, and further to provide a pharmaceutical effect or to treat a disease, including HIV. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the ribozyme *in vivo*, as well as the determination of a vector that would provide an effective and sustained expression of the ribozyme, to provide a pharmaceutical effect. Given the art recognized unpredictability of the therapeutic application of ribozymes and gene therapy *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the state of the art of ribozyme and gene therapy treatments, the level of unpredictability of *in vivo* (whole organism) methods of treatment using ribozymes and gene therapy, the lack of specific guidance for the *in vivo* (whole organism) application of the claimed methods and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods claimed or make the claimed pharmaceutical compositions over the full scope claimed without undue trial and error experimentation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
March 24, 2003

Karen Lacourciere
KAREN LACOURCIERE
PATENT EXAMINER